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Peskoe, Sarah B ; Joshu, Corinne E ; Rohrmann, Sabine ; McGlynn, Katherine A ; Nyante, Sarah J ; Bradwin, Gary ; Dobs, Adrian S ; Kanarek, Norma ; Nelson, William G ; Platz, Elizabeth A

Abstract: BACKGROUND The association between serum sex steroid hormones and PSA in a general population has not been described. METHODS Included were 378 men aged 40-85 years who participated in the National Health and Nutrition Examination Survey in 2001-2004, who did not have a prostate cancer diagnosis, and had not had a recent biopsy, rectal examination, cystoscopy, or prostate infection or inflammation. Serum total PSA, total testosterone, androstanediol glucuronide (3 -diol-G), estradiol, and sex hormone binding globulin (SHBG) concentrations were previously measured. Free testosterone was estimated by mass action. We applied sampling weights and calculated geometric mean PSA concentration by hormone quintiles adjusting for age and race/ethnicity, and also for body mass index, waist circumference, smoking, diabetes, and mutually for hormones. We estimated the OR of PSA 2.5 ng/ml per hormone quintile using logistic regression. RESULTS Geometric mean PSA increased across testosterone quintiles after age and race/ethnicity (Q1: 0.80, Q5: 1.14 ng/ml; P-trend = 0.002) and multivariable (Q1: 0.79, Q5: 1.16 ng/ml; P-trend = 0.02) adjustment; patterns were similar for free testosterone and 3 -diol-G. SHBG was inversely associated with PSA only after multivariable adjustment (Q1: 1.32, Q5: 0.82 nmol/L; P-trend = 0.01). Estradiol and PSA were not associated. The OR of PSA 2.5 ng/ml was 1.54 (95% CI 1.18-2.01) per testosterone quintile after age and race/ethnicity adjustment, and 1.78 (95% CI 1.16-2.73) after multivariable adjustment. CONCLUSIONS In this nationally representative sample, men with higher testosterone had higher PSA even after taking into account other hormones and modifiable factors. Men with higher SHBG had lower PSA, but only after multivariable adjustment.

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Circulating Total Testosterone and PSA Concentrations in a Nationally Representative Sample of Men Without a Diagnosis of Prostate Cancer

Sarah B. Peskoe[1], **Corinne E. Joshu**[1], **Sabine Rohrmann**[2], **Katherine A. McGlynn**[3], **Sarah J. Nyante**[3], **Gary Bradwin**[4], **Adrian S. Dobs**[5,6], **Norma Kanarek**[6,7], **William G. Nelson**[6,7,8], and **Elizabeth A. Platz**[1,6,8]

[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA [2]Department of Chronic Disease Epidemiology; Epidemiology, Biostatistics and Prevention Institute (EBPI), University of Zurich, Zurich, Switzerland [3]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA [4]Department of Laboratory Medicine, Harvard Medical School and Children's Hospital, Boston, MA, USA [5]Division of Endocrinology and Metabolism, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA [6]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA [7]Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA [8]Department of Urology and the James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Abstract

Background—The association between serum sex steroid hormones and PSA in a general population has not been described.

Methods—Included were 378 men aged 40-85 years who participated in the National Health and Nutrition Examination Survey in 2001-2004, who did not have a prostate cancer diagnosis, and had not had a recent biopsy, rectal examination, cystoscopy, or prostate infection or inflammation. Serum total PSA, total testosterone, androstanediol glucuronide (3α-diol-G), estradiol, and sex hormone binding globulin (SHBG) concentrations were previously measured. Free testosterone was estimated by mass action. We applied sampling weights and calculated geometric mean PSA concentration by hormone quintiles adjusting for age and race/ethnicity, and also for body mass index, waist circumference, smoking, diabetes, and mutually for hormones. We estimated the OR of PSA ≥2.5 ng/mL per hormone quintile using logistic regression.

Results—Geometric mean PSA increased across testosterone quintiles after age and race/ethnicity (Q1: 0.80, Q5: 1.14 ng/mL; P-trend=0.002) and multivariable (Q1: 0.79, Q5: 1.16 ng/mL; P-trend=0.02) adjustment; patterns were similar for free testosterone and 3α-diol-G. SHBG was inversely associated with PSA only after multivariable adjustment (Q1: 1.32, Q5: 0.82

Address correspondence to: Elizabeth Platz, ScD, MPH, Department of Epidemiology, Room E6132, Johns Hopkins Bloomberg School of Public Health, 615 N Wolfe St., Baltimore, MD 21205; tel: 410-614-9674; fax: 410-614-2632; eplatz1@jhu.edu.

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nmol/L; P-trend=0.01). Estradiol and PSA were not associated. The OR of PSA ≥2.5 ng/mL was 1.54 (95% CI 1.18-2.01) per testosterone quintile after age and race/ethnicity adjustment, and 1.78 (95% CI 1.16-2.73) after multivariable adjustment.

Conclusions—In this nationally representative sample, men with higher testosterone had higher PSA even after taking into account other hormones and modifiable factors. Men with higher SHBG had lower PSA, but only after multivariable adjustment.

Keywords

testosterone; prostate specific antigen; men

Introduction

Prostate specific antigen (PSA)-based prostate cancer screening is controversial, in part, because of imperfect specificity, especially for aggressive disease [1]. PSA production by prostate luminal epithelial cells is under androgenic regulation [2]. However, the association between circulating androgen and PSA levels is unclear in general populations of men. Thus, we investigated the association between serum concentrations of total PSA and androgens – total testosterone, free testosterone, and androstanediol glucuronide (3α-diol-G) – in men without a prostate cancer diagnosis in the continuous National Health and Nutrition Examination Survey (NHANES), a nationally representative sample of non-institutionalized Americans. We also investigated the association of estradiol and sex hormone binding globulin (SHBG), which carries both testosterone and estradiol in circulation, with PSA in these men. We hypothesized that men with higher circulating concentrations of total testosterone, free testosterone, and 3α-diol-G, and lower concentrations of SHBG and estradiol would have a higher PSA. Knowledge of this association may be used in the future to enhance clinical decision-making for an elevated screening serum PSA.

Materials and Methods

Study population

NHANES is a series of cross-sectional studies conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention [3]. By design, each cycle of NHANES is representative of the total civilian non-institutionalized population of adults and children aged two months or older in the United States. It utilizes a multistate stratified probability sample and includes an oversampling of Hispanics, non-Hispanic blacks and the elderly to allow for more precise estimates in these subgroups. This analysis included men from two cycles of continuous NHANES, 2001-2002 and 2003-2004. Unbiased national estimates of health and nutritional characteristics can be independently produced for each cycle.

As part of NHANES 2001-2002 and 2003-2004, serum total PSA concentration was measured in men who were at least 40 years of age, who consented, and who did not have a past prostate cancer diagnosis, recent biopsy, rectal examination, or cystoscopy, or current infection or inflammation of the prostate. Serum for sex steroid hormone concentrations was measured in a sub-sample of men at least 20 years of age and who participated in the

morning examination session in NHANES 1999-2004 [4]. The overlap between the measurement of PSA and hormone concentrations was 410 men who were aged 40-85 years. We excluded 23 men with missing baseline characteristics (height, weight, waist circumference, smoking status, diabetes) and 9 men who had missing values for at least one of the sex steroid hormones that were measured. Thus, 378 men were included in the analysis.

Measurement of sex steroid hormone, SHBG, and PSA concentrations

Sex steroid hormone concentrations were measured in the laboratory of Dr. Nader Rifai (Children's Hospital, Boston, MA). Total testosterone, total estradiol, and SHBG concentrations were assayed using electrochemiluminescence immunoassays on the Elecsys 2010 autoanalyzer (Roche Diagnostics, Indianapolis, IN). Concentration of 3α-diol-G, a metabolite of dihydrotestosterone, was assayed using the direct 3α-Diol-G ELISA kit (ALPCO Diagnostics, Salem, NH); in this analysis we use 3α-diol-G as a surrogate for dihydrotestosterone. The assay limits of detection were: total testosterone (0.02 ng/mL), 3α-diol-G (0.33 ng/mL), total estradiol (5 pg/mL), and SHBG (3 nmol/L). Coefficients of variation for 21 samples assayed in duplicate were: 4.8% for total testosterone, 9.7% for 3α-diol-G, 21.4% for total estradiol, and 5.6% for SHBG. All men had measured total testosterone, 3α-diol-G, and SHBG concentrations above their respective limits of detection. Four men had a measured estradiol concentration below the limit of detection; concentration was imputed by modeling the distribution of estradiol concentrations above 5 pg/mL, extrapolating this distribution below the limit of detection, and randomly sampling values between 0 and 5 pg/mL from the extrapolated probability distribution. Free testosterone was calculated from the total testosterone, SHBG and serum albumin (measured using the Bromcresol Purple method) concentrations [5].

Serum total PSA concentration was measured using the Beckman Access Immunoassay System with the Hybritech Total PSA Assay (Beckman Coulter, Fullerton, CA) [6].

Measurement of covariates

Age, race/ethnicity, cigarette smoking and history of a diagnosis of type II diabetes mellitus were assessed by standardized in-home interview. Body height, body weight, waist circumference and fasting glucose were measured during a mobile medical examination center visit. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic (combined Mexican-American and other Hispanic), and Other. Cigarette smoking was categorized as never (men who smoked fewer than 100 cigarettes during their lifetime), former (men who smoked at least 100 cigarettes in their lifetime and reported that they now smoke ‘not at all’), and current smokers (men who smoked at least 100 cigarettes in their lifetime and reported they now smoke ‘every day’ or ‘some days’). We categorized men as non-diabetic (no diagnosis of diabetes from a doctor and fasting glucose <100 mg/dL), pre-diabetic (no diagnosis of diabetes from a doctor and fasting glucose between 100 and 125 mg/dL), and diabetic (diagnosis of diabetes from a doctor or fasting glucose >125 mg/dL). Body mass index (BMI, kg/m^2) was calculated from weight and height.

Statistical analysis

In all analyses we used the morning sampling weights to account for the NHANES complex survey design. We calculated demographic characteristics of the men, including age and race/ethnicity, and age- and race/ethnicity-adjusted BMI, waist circumference, cigarette smoking status and diabetes across quintiles of total testosterone concentration. We estimated P-values for differences among quintiles from Wald chi-square tests for proportions and one-way ANOVAs for means. Additionally, we determined P-trends for mean age, BMI and waist circumference from a Wald F-test modeling total testosterone as a single ordinal variable based on quintile.

Because serum PSA concentration was not normally distributed, it was transformed using the natural logarithm. Then, we estimated geometric mean serum PSA concentration and 95% confidence interval by weighted quintile of concentrations of total testosterone, free testosterone, 3α-diol-G, estradiol, and SHBG. We evaluated the trend in geometric mean PSA concentration across hormone quintiles by modeling each hormone concentration as a single ordinal variable, assigning each man the median concentration within his quintile, and evaluating its statistical significance using the Student's T-test.

Age- and race/ethnicity- adjusted and multivariable-adjusted geometric means were estimated using predicted margins from linear regression models. Age in years, parameterized as a restricted quadratic spline with three knots at the 10^{th}, 50^{th} and 90^{th} percentiles, and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Other) were included in all models. Multivariable models were further adjusted for BMI (normal [<25 kg/m^2], overweight [25-29.9 kg/m^2], obese [≥30.0 kg/m^2]), waist circumference (<94 cm, 94 to <102 cm, ≥102 cm), cigarette smoking status (non-smoker, former smoker, current smoker), diabetes (non-diabetic, pre-diabetic, diabetic), and mutually for the other hormones as natural logarithm-transformed continuous variables (total testosterone: estradiol and SHBG; free testosterone: estradiol; 3α-diol-G: estradiol and SHBG; estradiol: total testosterone and SHBG; SHBG: total testosterone and estradiol).

We estimated multivariable-adjusted geometric mean serum PSA concentration by quintile of hormone concentration stratified by categories of race/ethnicity, adiposity (high: BMI above the median of 28 kg/m^2 or waist ≥102 cm; low: BMI at or below the median of 28 kg/m^2 and waist circumference <102 cm [7]), and age (younger: at or above the median of 52 years, older: >52 years). Stratum-specific estimates were generated using a common model, allowing for the comparison across strata (e.g., geometric means for PSA by total testosterone quintiles can be compared across non-Hispanic whites, non-Hispanic blacks, and Hispanics, etc.). We tested for interactions by including the main effects terms for the hormone and the stratification factor, along with a term for their product, the coefficient for which was evaluated by conducting a Wald test.

Serum PSA concentration was categorized into higher and lower concentrations with cutpoints at 4.0, 2.5, and 2.0 ng/mL; these cutpoints were selected because 4.0 ng/mL is the most commonly used cutpoint for biopsy recommendation and these cutpoints yield different prostate cancer detection rates [8]. Multivariable logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) of higher serum PSA

concentration across quintiles of total testosterone concentration. We evaluated the trend in elevated serum PSA across hormone quintiles by modeling total testosterone concentration as a single ordinal variable, assigning each man the median concentration within his quintile, and evaluating its statistical significance using the Student's t-test. Statistical analyses were performed using Stata 12 (College Station, TX), SAS 9.3 (Cary, NC) and SUDAAN 10 (Research Triangle Park, NC).

Results

Characteristics of the men

Characteristics of the 378 men are presented in Table I, both overall and by quintile of total testosterone concentration. The men had a mean age of 54.8 years and 79.0% were white. Mean BMI was 28.6 kg/m^2 and mean waist circumference was 103.0 cm. Most men were overweight or obese (75.9%), 62.2% were current or former smokers, and 51.4% were diabetic or pre-diabetic.

In Table I, cross-sectionally, mean age decreased across quintiles of total testosterone (P-trend=0.005). The overall age-adjusted distribution of race/ethnicity differed across quintiles of total testosterone (P<0.0001). After adjusting for age and race/ethnicity, mean BMI and mean waist circumference decreased across quintiles of total testosterone (both P-trend<0.0001). Prevalence of current and former smoking (P<0.0001) and diabetes (P<0.0001) also differed across quintiles of total testosterone after adjusting for age and race/ethnicity.

Association between sex steroid hormone concentrations and PSA

Geometric mean serum PSA concentration by quintiles of total testosterone, free testosterone, 3α-diol-G, estradiol and SHBG after age and race/ethnicity adjustment and after further multivariable adjustment is shown in Table II. PSA concentration increased across quintiles of total testosterone (P-trend=0.002), free testosterone (P-trend<0.001), and 3α-diol-G (P-trend=0.01) after age and race/ethnicity adjustment. These same patterns were observed after further multivariable adjustment for total testosterone (P-trend=0.02), free testosterone (P-trend=0.03), and 3α-diol-G (P-trend=0.002). While PSA concentration was not associated with SHBG after age and race/ethnicity adjustment (P-trend=0.93), it was inversely associated after multivariable adjustment (P-trend=0.01). Adjustment for total testosterone concentration explained the shift, which we determined by entering each covariate one at a time into the model along with age and race/ethnicity. There was no statistically significant pattern in PSA concentration across quintiles of estradiol. Given the similar patterns in PSA across quintiles of total testosterone, free testosterone, and 3α-diol-G (Figure), we focused on the association between total testosterone and PSA for the remainder of the study.

Stratified analyses

Table III shows multivariable-adjusted geometric mean serum PSA concentration by quintiles of total testosterone stratified by categories of race/ethnicity, adiposity, and age. Overall, Hispanic men had the lowest total testosterone concentration and non-Hispanic

whites had the highest. PSA concentration increased across total testosterone quintiles in non-Hispanic whites (P-trend=0.02) and non-Hispanic blacks (P-trend=0.008). Although not statistically significant, this same pattern was observed in Hispanic men. There was no interaction between race/ethnicity and total testosterone (P-interaction=0.85).

Men with lower adiposity (BMI ≤28.02 kg/m^2 and waist circumference <102 cm) had overall higher levels of PSA than men with higher adiposity; however, the same increasing pattern in PSA was observed across quintiles of total testosterone in both groups (P-trend=0.004 and 0.02, respectively). There was no interaction between adiposity and total testosterone (P-interaction=0.65).

PSA concentration increased across quintiles of total testosterone among older men (>52 years, P-trend=0.01), and was higher than in younger men. Although not significant, this same increasing pattern was also observed in younger men. There was a possible interaction between age and total testosterone (P-interaction=0.06).

Odds of higher serum PSA concentration

ORs of higher PSA were estimated across quintiles of total testosterone after age- and race/ethnicity-adjustment and after further multivariable-adjustment (Table IV). Men with higher total testosterone levels were more likely to have a PSA >4.0, >2.5, and >2.0 ng/mL than those with lower total testosterone levels.

Discussion

In this nationally representative, cross-sectional sample of US men aged 40+ years old without a prostate cancer diagnosis, those with a higher serum total testosterone concentration had higher serum total PSA concentration taking into account age, race/ethnicity, and other factors. We observed this same pattern of association between PSA and both free testosterone and 3α-diol-G. Serum SHBG concentration was associated with lower PSA concentration, but only after multivariable adjustment including for total testosterone. The odds of higher PSA were greater among men with higher total testosterone levels, including for the clinical cutpoint of 4.0 ng/mL. This suggests men in the general population who are of the target age for prostate cancer screening who have higher total testosterone levels may be at increased risk of unnecessary prostate biopsy due to an elevated PSA.

PSA is serine protease produced by prostate luminal epithelial cells [9]. While transcription of the PSA gene is transactivated by the androgen receptor with bound androgen, it is not clear whether circulating androgen influences circulating PSA. Indirect evidence for the influence of circulating androgens on PSA comes from the fact that men treated for prostate cancer with androgen deprivation therapy experience a decline in serum PSA concentration. This decline is probably due to both fewer cancer cells remaining to produce PSA, and substantially reduced testosterone available to all PSA-producing cells. Our study supports that even across the range of PSA in middle aged and older men without the diagnosis of prostate cancer, serum total testosterone concentration is positively associated with serum PSA concentration. This pattern was present for men across racial and ethnic groups, men who were leaner and heavier, and men who were younger and older.

Other investigators have reported on the link between testosterone and PSA concentrations, but none used a nationally representative sample of men. A pooled analysis of prospective epidemiologic studies on hormones and prostate cancer found that, among controls, baseline PSA concentration was weakly positively correlated with free testosterone concentration (6,479 men, r=0.11), but not with total testosterone (7,143 men, r=0.08), other androgens, estradiol, free estradiol, or SHBG [10] when taking into account age; detailed analyses were not performed. In men with sexual dysfunction, Corona et al. [11] found that those who were in the lowest decile of total testosterone had a lower PSA concentration when compared to all other men, otherwise, no dose-response across testosterone concentration was observed. This same pattern was present also in the subset of these men free of prostate diseases. Also in men with sexual dysfunction, but restricting to PSA concentration <4 ng/mL, Rastrelli et al. [12] found that men with total testosterone <8 nmol/L were more likely to have a low PSA concentration (<0.65 ng/mL) than men with higher total testosterone. In contrast, in men referred for prostate biopsy for an elevated PSA or abnormal digital rectal examination, Botelho et al. [13] reported that total testosterone concentration was not correlated with total PSA. While these studies taken together support that circulating levels of androgens and PSA are related to some extent, our study specifically fills the gap in understanding the link between circulating androgens and PSA in a general population of men not enriched for clinical states that may distort the association.

To our knowledge, this is the first nationally representative study of circulating sex steroid hormones and PSA in adult males without prostate cancer or acute conditions (e.g., symptomatic prostatitis or prostate infection) or recent procedures that affect PSA concentration. NHANES participants are selected using a complex stratified, multistage, probability-cluster design insuring that the sample is representative of the general US population and not just those seeking screening. We included only men who participated in the morning session to minimize the influence of diurnal testosterone production. We were able to conduct analyses that took into account potential confounders and analyses that were restricted to important subgroups, including three major race/ethnicity groups in US.

Some of the men had PSA concentrations in the elevated range (5.2% of the men had PSA >4 ng/mL). We do not know whether any of these men were later diagnosed with prostate cancer. Further, among the men with PSA ≤4 ng/mL, we do not know who may have had occult prostate cancer. Also, we could not assess the relative contributions of androgens versus asymptomatic intraprostatic inflammation [14] to serum PSA. However, not having excluded men with prostate cancer or asymptomatic inflammation does not affect the inferences from our findings because our goal was to describe the hormone-PSA link in men in the general population and perhaps to be able to inform prostate cancer screening algorithms.

The measurement of total testosterone concentration was done with good precision and sensitivity by competitive electrochemiluminescence immunoassay. We did not use the more sensitive, but more expensive methods of gas or liquid chromatography coupled with mass spectrometry. The calculation of free testosterone was done using published formulae that provide well-documented correlation with the values of directly measured assays [15]; some noise in its estimation may have occurred due to the imperfect specificity of the

measurement of albumin by the Bromcresol Purple method [16]. However, we were still able to detect a positive association. While the precision in the measurement of estradiol concentration was somewhat lower than for the other hormones, we did not find differences in PSA concentrations even when comparing the highest and lowest quintiles of estradiol, suggesting no major influence on PSA. We measured hormones and PSA only once for each man, and as such the concentrations may not represent the men's usual levels over time. Finally, this study was cross-sectional, thus we could not determine the relationship between changing testosterone concentration (e.g., with aging or weight gain) and changing PSA concentration.

Conclusions

In summary, in this nationally representative sample of middle-aged and older men, those with higher total testosterone and 3α-diol-G in circulation had higher PSA in circulation, even after taking into account age and other factors. At this time we are not suggesting that men should have their serum testosterone concentration measured. However, we envision that knowledge of the size of this association may be used in the future to enhance tools for clinical decision-making following an elevated screening PSA.

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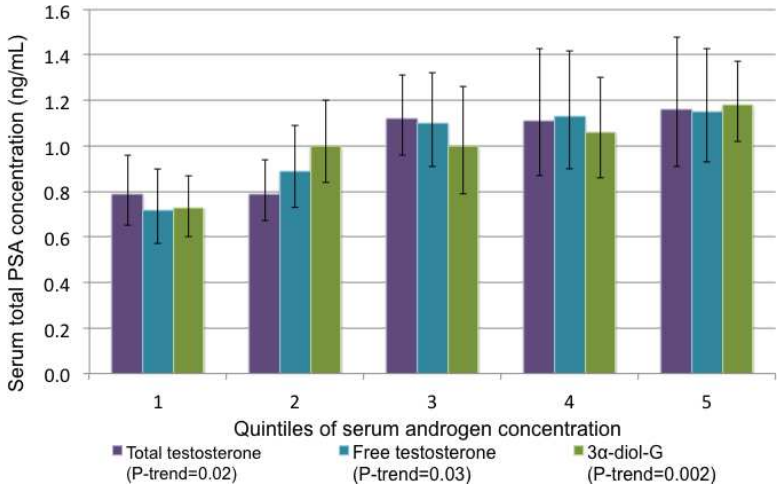

Figure.

Geometric mean* serum total PSA concentration by circulating androgen concentrations, 378 men, 40-85 years old, NHANES 2001-2004.

Table I

Age- and race/ethnicity-adjusted characteristics of 378 men aged 40-85 years old by serum total testosterone concentration, NHANES 2001-2004

	Overall	Quintile of Total Testosterone (ng/mL)						
		< 3.16	3.16 - < 4.04	4.04 - < 4.88	4.88 - < 6.02	≥6.02	P*	P-trend†
Number of men	378	89	75	61	75	78		
Mean ± SE age	54.8 ± 0.6	58.8 ± 2.0	56.0 ± 1.7	51.8 ± 1.3	54.3 ± 1.1	53.2 ± 1.0	0.03	0.005
Race/ethnicity (%)‡								
NH White	79.0	75.3	76.8	89.6	74.4	77.8		
NH Black	7.8	7.5	6.5	4.6	6.6	13.6	<0.0001	--
Hispanic	8.5	10.5	12.6	4.4	8.3	7.5		
Other	4.7	6.7	4.1	1.4	10.7	1.1		
Mean ± SE BMI (kg/m^2)§	28.6 ± 0.4	32.5 ± 1.2	28.3 ± 0.6	28.9 ± 0.7	27.4 ± 0.6	25.8 ± 0.5	0.0003	< 0.0001
BMI category (%)‡								
Underweight	0.5	0.3	1.6	0.0	0.0	0.7		
Normal	23.6	6.2	16.7	17.0	41.2	38.1	<0.0001	--
Overweight	44.0	35.9	57.6	46.9	33.6	45.8		
Obese	31.9	57.6	24.1	36.1	25.2	15.4		
Mean ± SE waist circumference (cm)§	103.0 ± 0.8	112.0 ± 2.1	103.6 ± 1.1	104.0 ± 2.0	99.6 ± 1.3	95.4 ± 1.4	< 0.0001	< 0.0001
Cigarette smoking status (%)§								
Non-smoker	37.8	39.7	46.7	41.8	38.8	24.7		
Former smoker	33.5	50.7	36.9	29.4	21.1	28.6	< 0.0001	--
Current Smoker	28.7	9.6	16.4	28.8	40.1	46.7		
Type II diabetes (%)§								
Non-diabetic	48.6	41.9	37.3	46.8	56.3	60.6		
Pre-diabetic	34.8	34.1	46.8	30.3	29.3	34.7	< 0.0001	--
Diabetic	16.6	24.0	15.9	22.9	14.4	4.7		

*Test for differences among quintiles of total testosterone from a Wald chi-square test for proportions or one-way ANOVA for means

†Test for trend across quintiles of total testosterone from a Wald F-test

‡Quintile estimates adjusted for age in years (continuous)

§Quintile estimates adjusted for age in years (continuous) and race/ethnicity (NH White, NH Black, Hispanic, Other)

Table II

Adjusted geometric mean serum total PSA concentration by quintile of serum sex steroid hormone concentrations, 378 men, 40-85 years old, NHANES 2001-2004

Quintiles of sex steroid hormone concentrations	*N*	Geometric mean serum total PSA concentration in ng/mL (95% CI)	
		Age and race/ethnicity adjusted*	Multivariable adjusted†
Total testosterone (ng/mL)			
< 3.16	89	0.80 (0.67, 0.95)	0.79 (0.65, 0.96)
3.16 - < 4.04	75	0.82 (0.68, 0.98)	0.79 (0.67, 0.94)
4.04 - < 4.88	61	1.11 (0.94, 1.31)	1.12 (0.96, 1.31)
4.88 - < 6.02	75	1.09 (0.86, 1.39)	1.11 (0.87, 1.43)
≥6.02	78	1.14 (1.00, 1.30)	1.16 (0.91, 1.48)
P-trend‡		0.002	0.02
Free testosterone (ng/mL)			
< 0.0586	96	0.68 (0.56, 0.82)	0.72 (0.57, 0.90)
0. 0586- < 0.0757	87	0.88 (0.72, 1.08)	0.89 (0.73, 1.09)
0. 0757- < 0.0921	68	1.10 (0.91, 1.33)	1.10 (0.91, 1.32)
0.0921 - < 0.1117	66	1.16 (0.93, 1.45)	1.13 (0.90, 1.42)
≥0.1117	61	1.19 (1.00, 1.40)	1.15 (0.93, 1.43)
P-trend‡		< 0.001	0.03
Androstanediol glucuronide (ng/mL)			
< 4.79	88	0.72 (0.60, 0.86)	0.73 (0.60, 0.87)
4.79 - < 5.99	76	1.03 (0.87, 1.22)	1.00 (0.84, 1.20)
5.99 - < 7.79	84	1.02 (0.83, 1.24)	1.00 (0.79, 1.26)
7.79 - < 10.21	63	1.05 (0.85, 1.31)	1.06 (0.86, 1.30)
≥10.21	67	1.14 (0.96, 1.36)	1.18 (1.02, 1.37)
P-trend‡		0.01	0.002
Total estradiol (pg/mL)			
< 20.60	94	0.93 (0.74, 1.17)	1.00 (0.81, 1.23)
20.60 - < 27.43	70	0.85 (0.73, 0.99)	0.93 (0.79, 1.10)
27.43 - < 33.48	69	1.15 (0.96, 1.39)	1.22 (1.00, 1.49)
33.48 - < 43.64	83	0.89 (0.73, 1.07)	0.84 (0.71, 1.00)
≥43.64	62	1.11 (0.95, 1.30)	0.95 (0.76, 1.17)
P-trend‡		0.20	0.64
Sex hormone binding globulin (nmol/L)			
< 24.14	59	1.01 (0.79, 1.29)	1.32 (1.01, 1.71)
24.14 - < 32.96	74	0.99 (0.84, 1.17)	1.07 (0.91, 1.26)
32.96 - < 41.03	66	1.12 (0.93, 1.36)	1.10 (0.92, 1.32)
41.03 - < 51.95	73	0.78 (0.65, 0.93)	0.71 (0.60, 0.83)
≥51.95	106	1.04 (0.81, 1.35)	0.82 (0.66, 1.02)
P-trend‡		0.93	0.01

[*] Adjusted for age in years (spline) and race/ethnicity (NH White, NH Black, Hispanic, Other).

[†] Adjusted for age in years (spline), race/ethnicity (NH White, NH Black, Hispanic, Other), body mass index (categorical), waist circumference (continuous), cigarette smoking status (non-smoker, former smoker, current smoker), type II diabetes (non-diabetic, pre-diabetic, diabetic), and mutually for the other hormones (total testosterone: estradiol and sex hormone binding globulin (SHBG), free testosterone: estradiol, androstanediol glucuronide: estradiol and SHBG, estradiol: total testosterone and SHBG, SHBG: total testosterone and estradiol; continuous, natural logarithm-transformed).

[‡] P-trend calculated modeling natural logarithm-transformed PSA concentration and median hormone concentration by quintile.

Table III

Multivariable-adjusted geometric mean serum total PSA concentration by quintile of serum total testosterone concentration and stratified by race/ethnicity, adiposity, and age, 378 men, 40-85 years old, NHANES 2001-2004

Quintile of serum total testosterone concentration (ng/mL)	Geometric mean serum total PSA concentration (ng/mL)													
	Race/ethnicity*						Adiposity†				Age‡			
	NH White		NH Black		Hispanic		Higher		Lower		Younger (≤52 years)		Older (> 52 years)	
N	Mean (95% CI)	*N*	Mean (95% CI)	*N*	Mean (95% CI)	*N*	Mean (95% CI)	*N*	Mean (95% CI)	*N*	Mean (95% CI)	*N*	Mean (95% CI)	
< 3.16	51	0.79 (0.64, 0.97)	11	0.89 (0.69, 1.15)	24	0.70 (0.53, 0.92)	66	0.73 (0.59, 0.90)	23	0.79 (0.65, 0.96)	21	0.61 (0.27, 1.36)	68	1.02 (0.43, 2.43)
3.16 - < 4.04	45	0.79 (0.65, 0.95)	11	0.89 (0.70, 1.13)	17	0.70 (0.54, 0.91)	47	0.77 (0.65, 0.91)	28	0.83 (0.67, 1.02)	26	0.62 (0.28, 1.38)	49	1.04 (0.44, 2.46)
4.04 - < 4.88	40	1.11 (0.94, 1.31)	7	1.26 (1.04, 1.54)	13	0.99 (0.74, 1.33)	37	1.08 (0.91, 1.29)	24	1.17 (0.98, 1.39)	29	0.88 (0.39, 1.97)	32	1.48 (0.63, 3.45)
4.88 - < 6.02	38	1.11 (0.87, 1.41)	12	1.26 (0.95, 1.67)	21	0.99 (0.70, 1.39)	34	1.09 (0.86, 1.39)	41	1.18 (0.91, 1.53)	30	0.86 (0.39, 1.91)	45	1.45 (0.59, 3.58)
≥6.02	41	1.15 (0.90, 1.47)	20	1.31 (1.00, 1.73)	16	1.03 (0.74, 1.42)	28	1.16 (0.88, 1.54)	50	1.25 (0.96, 1.63)	40	0.91 (0.41, 2.00)	38	1.52 (0.61, 3.76)
P-trend§		0.02		0.008		0.15		0.02		0.004		0.31		0.01
P-interaction**				0.85				0.65				0.06		

*Adjusted for age in years (spline), body mass index (BMI; categorical), waist circumference (continuous), cigarette smoking status (non-smoker, former smoker, current smoker), type II diabetes (non-diabetic, pre-diabetic, diabetic), estradiol (continuous, natural logarithm-transformed), sex hormone binding protein (SHBG; continuous, natural logarithm-transformed).

†Adiposity determined as high: waist circumference ≥102 cm or BMI > median (28.02 kg/m^2), or low: waist circumference < 102 and BMI ≤median (28.02 kg/m^2). PSA adjusted for age in years (spline), race/ethnicity (NH White, NH Black, Hispanic, Other), smoking status (non-smoker, former smoker, current smoker), type II diabetes (non-diabetic, pre-diabetic, diabetic), estradiol (continuous, natural logarithm-transformed), SHBG (continuous, natural logarithm-transformed).

‡Cutpoint at the median age. PSA adjusted for within-stratum age (continuous) race/ethnicity (NH White, NH Black, Hispanic, Other), BMI (categorical), waist circumference (continuous), smoking status (non-smoker, former smoker, current smoker), type II diabetes (non-diabetic, pre-diabetic, diabetic), estradiol (continuous, natural logarithm-transformed), SHBG (continuous, natural logarithm-transformed).

§P-trend calculated modeling the natural logarithm-transformed PSA concentration, and median total testosterone concentration by quintile.

**P-interaction calculated modeling the main effects of the hormone and the stratification factor, along with a term for their product, the coefficient for which was evaluated by conducting a Wald test.

Table IV

Odds ratio (OR) of higher serum total PSA concentration by quintile of serum total testosterone concentration, 378 men, 40-85 years old, NHANES 2001-2004

Quintile of serum total testosterone concentration (ng/mL)	*N*	OR of higher serum total PSA concentration (95% CI)	
		Age and race/ethnicity adjusted*	Multivariable adjusted†
PSA concentration > 4.0 ng/mL (5.2%)			
< 3.16	89	1.00 (reference)	1.00 (reference)
3.16 - < 4.04	75	2.14 (0.45, 10.14)	1.98 (0.34, 11.71)
4.04 - < 4.88	61	5.85 (0.71, 47.96)	5.43 (0.42, 70.95)
4.88 - < 6.02	75	5.88 (1.32, 26.21)	6.61 (1.22, 35.65)
≥6.02	78	7.04 (1.23, 40.36)	5.54 (0.49, 62.90)
Per quintile increase		1.57 (1.07, 2.31)	1.56 (0.95, 2.56)
P-trend‡		0.02	0.10
PSA concentration ≥2.5 ng/mL (11.3%)			
< 3.16	89	1.00 (reference)	1.00 (reference)
3.16 - < 4.04	75	1.63 (0.47, 5.60)	1.71 (0.46, 6.40)
4.04 - < 4.88	61	2.66 (0.62, 11.54)	3.41 (0.55, 21.08)
4.88 - < 6.02	75	3.08 (0.98, 9.67)	4.88 (1.17, 20.32)
≥6.02	78	6.33 (2.23, 17.99)	11.14 (1.84, 67.29)
Per quintile increase		1.54 (1.18, 2.01)	1.78 (1.16, 2.73)
P-trend‡		0.001	0.006
PSA concentration ≥2.0 ng/mL (15.8%)			
< 3.16	89	1.00 (reference)	1.00 (reference)
3.16 - < 4.04	75	1.17 (0.26, 5.30)	1.10 (0.23, 5.16)
4.04 - < 4.88	61	3.58 (0.64, 20.17)	3.79 (0.61, 23.60)
4.88 - < 6.02	75	2.08 (0.33, 13.06)	2.66 (0.45, 15.81)
≥6.02	78	3.62 (0.73, 17.86)	4.48 (0.74, 27.16)
Per quintile increase		1.35 (0.95, 1.91)	1.44 (0.97, 2.12)
P-trend‡		0.08	0.08

*Adjusted for age in years (spline) and race/ethnicity (NH White, NH Black, Hispanic, Other).

†Adjusted for age in years (spline), race/ethnicity (NH White, NH Black, Hispanic, Other), body mass index (categorical), waist circumference (continuous), cigarette smoking status (non-smoker, former smoker, current smoker), type II diabetes (non-diabetic, pre-diabetic, diabetic), estradiol (continuous, natural logarithm-transformed), sex hormone binding globulin (continuous, natural logarithm-transformed).

‡P-trend calculated modeling the natural logarithm-transformed PSA concentration and median total testosterone concentration by quintile.